CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074444

Trade Name : MICONAZOLE NITRATE VAGINAL CREAM 2%

Generic Name: Miconazole Nitrate Vaginal Cream 2%

Sponsor : Taro Pharmaceuticals, Inc.

Approval Date: January 13, 1997

ANDA 74-444

Taro Pharmaceuticals, Inc.
Attention: Timothy A. Anderson (U.S. Agent)
Taro Pharmaceuticals USA, Inc.
5 Skyline Drive
Hawthorne, NY 10532

Dear Sir:

This is in reference to your abbreviated new drug application dated December 20, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Miconazole Nitrate Vaginal Cream, 2%.

Reference is also made to your amendments dated October 16, October 30, November 7, 1995, October 4, and December 20, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted Over-The-Counter (OTC) labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Miconazole Nitrate Vaginal Cream, 2% to be bioequivalent to Monistat® 7 of RW Johnson Pharmaceutical Research Institute.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Sincerely yours,

1/13/97

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

Div. File

Supervisory Medical Officer's
Consult Memorandum
ANDA 74-444

Date: 24 May, 1996

To: Director, Office of Generic Drugs
HFD-615

From: Brad Leissa, MD
Supervisory Medical Officer, DAIDP (HFD-520)

Through: Mary Fanning, MD, PhD, FACP
Director, DAIDP (HFD-520)

RE: Taro Pharmaceutical, Inc.'s miconazole 2% vaginal cream ANDA

This application seeks ANDA approval for miconazole 2% vaginal cream in the treatment of women with vaginal candidiasis. The applicant submitted the data from a single study, #MCN1. Taro's generic product was compared to Ortho USA's and Ortho Canada's Monistat-7 (miconazole 2% vaginal cream) in a multicenter, double-blind, randomized, parallel study. Patients self-administered the vaginal cream nightly for 7 consecutive days.

In the applicant's presentation of their analysis, patients were assessed at two posttreatment visits: Visit 2 (study days 14-17) and visit 3 (study days 35-42). By visit 3, the **therapeutic cure** rate (combined clinical and mycologic cures) was 35/50 (70%) for Taro's miconazole 2% vaginal cream vs. 47/62 (76%) for Ortho USA's and 47/64 (73%) for Ortho Canada's active controls. Using the 90% confidence interval approach (corrected), the upper and lower limits around the difference between both the two study arms are {-21.5%, +9.9%} comparing the Taro product to the Ortho USA product. Conversely, the 90% CI between the Taro and Ortho Canada products is: {-19.2%, +12.4%}.

According to the reviewer's reanalysis of the submitted data, at visit 3, the therapeutic cure rate was 34/50 (68%) for Taro's product vs. 45/62 (73%) for Ortho USA's active control and 46/64 (72%) for Ortho Canada's active control. Based on the MO's reanalysis, using the 90% confidence interval approach (corrected), the upper and lower limits around the difference between the Taro and Ortho USA products are {-20.7%, +11.5%}. Conversely, the 90% CI between the Taro and Ortho Canada products is: {-19.9%, +12.2%}.

From a statistical standpoint, the applicant has failed to demonstrate therapeutic equivalence between Taro's miconazole 2% vaginal cream to Ortho's USA Monistat-7 2% cream, because the lower limit of the 90% confidence interval around the difference exceeds -20%.

Recommendation: This application is **not approvable**.

Brad Leissa, M.D.

CC: ANDA 74-444
HFD-630
HFD-340
HFD-520
HFD-520/MO/JPiver
HFD-520/SMO/BLeissa
HFD-520/Biostats/DLin
HFD-520/CSO/CChi

Concurrence Only:
HFD-520/Dir/MFanning

ANDA APPROVAL SUMMARY

ANDA: 74-444

DRUG PRODUCT: Miconazole Nitrate Vaginal Cream, 2%

FIRM: Taro Pharmaceuticals, Inc.

DOSAGE FORM: Cream **STRENGTH:** 2%

CGMP: An updated EER was issued on 7-12-96 and found acceptable on 12-31-97.

BIO: The firm has met the requirements of in **vivo** bioequivalency. The ANDA was reviewed and found acceptable on 12/10/96. The bio signoff sheet requires the signature of Dr. R. Williams, Director of OPS. He previously indicated that the bio is acceptable (Memo: R. Williams dated 11-24-96).

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

The bulk drug substance is a USP 23 listed compendial monograph and is certified to these requirements. The drug product is not compendial as a "vaginal cream" but meets the USP 23 compendial monograph requirements for "Miconazole Nitrate Cream". Two other ANDA's have been approved on this basis, i.e. 74-030 (Copley) and 74-136 (Lemmon).

STABILITY:

The containers in the stability study are identical to those in the container section.

LABELING:

Container, carton and insert labeling have been approved for this drug product (L. Golson, 5-24-96).

STERILIZATION VALIDATION (IF APPLICABLE):

Batch sterilization is not required for this drug product. However, Taro has established microbiological criteria for release and stability testing of this drug product.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

SIZE OF STABILITY BATCHES- (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The exhibit batch (lot E2I34) is the bio batch.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:

The proposed production batches The manufacturing process is the same as the exhibit batches.

CHEMIST: A.J. Mueller, Ph.D. **DATE:** January 8, 1997

SUPERVISOR: P. Schwartz, Ph.D. **DATE:** January 8, 1997

cc: ANDA #74-444
ANDA #74-444/Division File
Endorsements:
HFD-627/A.Mueller/1-8-97 A.J. Mueller 1-8-97
HFD-627/P.Schwartz, Ph.D./1-8-97
X:\NEW\FIRMSNZ\TARO\LTRS&REV\74444N05.D
F/T MM January 8, 1997

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO. 5 **Final Approval**

2. ANDA # 74-444

3. NAME AND ADDRESS OF APPLICANT
Taro Pharmaceuticals, Inc.
Attention: Timothy A. Anderson
5 Skyline Drive
Hawthorne, NY 10532

Tel: (914) 345-9001

4. LEGAL BASIS OF SUBMISSION:
No Patent or any marketing exclusivity rights are in effect.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Miconazole Nitrate Vaginal Cream, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Applicant:	
12/20/93	Original Submission
08/05/94	Amendment
02/28/95	Amendment
10/16/95	New Correspondence
10/30/95	New Correspondence
11/06/95	Amendment
11/07/95	New Correspondence
03/08/96	Amendment (CMC, Label)
05/03/96	Amendment (Label)
10-04-96	Amendment (CMC)
12-20-96	Amendment (withdrawal of FDC BDS supplier)
01-06-97	Amendment (response to stability questions)
FDA:	
05-03-94	NA Letter
11/18/94	NA Letter
02-01-96	NA Letter
08-01-96	NA Letter

10. PHARMACOLOGICAL CATEGORY
Anti-fungal

11. Rx or OTC
OTC

12. RELATED IND/NDA/DMF(s)

Reference Drug:	Miconazole Nitrate (Monistat 7®) 2%
Holder:	R. W. Johnson
NDA #	17450

13. DOSAGE FORM

Cream (Vaginal)

14. STRENGTH

2%

15. CHEMICAL NAME AND STRUCTURE

1H-Imidazole, 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-, mononitrate.
Mol formula $C_{18}H_{14}Cl_4N_2O.HNO_3$ Mol Wt 479.15

16. COMMENTS

No comments.

17. CONCLUSIONS AND RECOMMENDATIONS

This application is approvable, pending an acceptable EER from the Office of Compliance, DMPQ.

18. RECORDS AND REPORTS

N/A

19. REVIEWER: DATE COMPLETED:

A.J. Mueller, Ph.D. January 8, 1997

Endorsed by P. Schwartz, Ph.D. January 8, 1997

PK-1366-0

EDUCATIONAL BROCHURE

MICONAZOLE NITRATE VAGINAL CREAM 2%

7 DAY VAGINAL CREAM
CURES MOST VAGINAL YEAST INFECTIONS
AND RELIEVES ASSOCIATED EXTERNAL VULVAR ITCHING AND IRRITATION

JAN 13 1997

INDICATIONS:

For the treatment of vaginal yeast infections (candidiasis) and the relief of external vulvar itching and irritation associated with a yeast infection.

If you have any or all of the symptoms of a vaginal yeast infection (vaginal itching, burning, discharge) and if at some time in the past your doctor has told you that these symptoms are due to a vaginal yeast infection, then miconazole nitrate vaginal cream should work for you. If, however, you have never had these symptoms before, you should see your doctor before using miconazole nitrate vaginal cream.

MICONAZOLE NITRATE VAGINAL CREAM IS FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS AND FOR THE RELIEF OF EXTERNAL VULVAR ITCHING AND IRRITATION ASSOCIATED WITH A YEAST INFECTION. IT DOES NOT TREAT OTHER INFECTIONS OR EXTERNAL ITCHING AND IRRITATION DUE TO CAUSES OTHER THAN YEAST INFECTIONS. IT DOES NOT PREVENT PREGNANCY.

WHAT ARE VAGINAL YEAST INFECTIONS (CANDIDIASIS)?

A yeast infection is a common type of vaginal infection. Your doctor may call it candidiasis. This condition is caused by an organism called Candida, which is a type of yeast. Even healthy women usually have this yeast on the skin, in the mouth, in the digestive tract, and in the vagina. At times, the yeast can grow very quickly. In fact, the infection is sometimes called yeast (Candida) "overgrowth". Some women also experience a yeast infection on the external skin (vulva) associated with the internal vaginal infection.

A yeast infection can occur at almost any time of life. It is most common during the childbearing years. The infection tends to develop most often in some women who are pregnant, diabetic, taking antibiotics, taking birth control pills, or have a damaged immune system.

Various medical conditions can damage the body's normal defenses against infection. One of the most serious of these conditions is infection with the human immunodeficiency virus (HIV - the virus that causes AIDS). Infection with HIV causes the body to be more susceptible to infections, including vaginal yeast infections. Women with HIV infection may have frequent vaginal yeast infections or, especially, vaginal yeast infections that do not clear up easily with proper treatment. If you may have been exposed to HIV and are experiencing either frequently recurring vaginal yeast infections or, especially, vaginal yeast infections that do not clear up easily with proper treatment, you should see your doctor promptly. If you wish further information on risk factors for HIV infection or on the relationship between recurrent or persistent vaginal yeast infections and HIV infection, please contact your doctor or the CDC National AIDS HOTLINE at 1-800-342-AIDS (English), 1-800-344-7432 (Spanish), or 1-800-243-7889 (hearing impaired, TDD).

IF YOU EXPERIENCE FREQUENT YEAST INFECTIONS (THEY RECUR WITHIN A TWO MONTH PERIOD), OR IF YOU HAVE YEAST INFECTIONS THAT DO NOT CLEAR UP EASILY WITH PROPER TREATMENT, YOU SHOULD SEE YOUR DOCTOR PROMPTLY TO DETERMINE THE CAUSE AND TO RECEIVE PROPER MEDICAL CARE.

SYMPTOMS OF VAGINAL YEAST INFECTIONS:

There are many signs and symptoms of a vaginal yeast infection. They can include:

- Vaginal itching (ranging from mild to intense);
- A clumpy, vaginal discharge that may look like cottage cheese;
- Vaginal soreness, irritation, or burning, especially during vaginal intercourse;
- Rash or redness around the vagina (vulvar irritation).

NOTE: Vaginal discharge that is different from above, for example, a yellow/green discharge or a discharge that smells "fishy", may indicate that you have something other than a yeast infection. If this is the case, you should consult your doctor before using miconazole nitrate vaginal cream.

WARNINGS

- This product is only effective in treating vaginal infection caused by yeast and in relieving vulvar itching and irritation associated with a yeast infection. Do not use in eyes or take by mouth.
- **Do not use miconazole nitrate vaginal cream if you have any of the following signs and symptoms. Also, if they occur while using miconazole nitrate vaginal cream, STOP using the product and contact your doctor right away. You may have a more serious illness.**
- **Fever (above 100°F orally).**
- **Pain in the lower abdomen, back or either shoulder.**
- **A vaginal discharge that smells bad.**
- If there is no improvement or if the infection worsens within 3 days, or complete relief is not felt within 7 days, or your symptoms return within two months, then you may have something other than a yeast infection. You should consult your doctor.
- If you may have been exposed to the human immunodeficiency virus (HIV, the virus that causes AIDS) and are now having recurrent vaginal infections, especially infections that don't clear up easily with proper treatment, see your doctor promptly to determine the cause of your symptoms and to receive proper medical care.
- Mineral oil may weaken latex in condoms or in diaphragms. This cream contains mineral oil. Do not rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy while using miconazole nitrate vaginal cream.
- Do not use tampons while using this medication.
- Do not use in girls less than 12 years of age.
- If you are pregnant or think you may be, do not use this product except under the advice and supervision of a doctor.
- Keep this and all drugs out of the reach of children.
- In case of accidental ingestion, seek professional assistance or contact a poison control center immediately.

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CONTENTS:

One tube of vaginal cream containing miconazole nitrate 2%. One reusable plastic applicator.

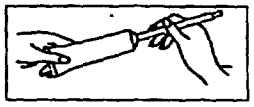
IMPORTANT: UNSCREW THE CAP. THE TUBE OPENING SHOULD BE SEALED. DO NOT USE IF SEAL IS PUNCTURED OR NOT VISIBLE AND RETURN PRODUCT TO PLACE OF PURCHASE.
TO PUNCTURE THE SEAL, REVERSE THE CAP AND PLACE THE PUNCTURE-TOP ONTO THE TUBE. PUSH DOWN FIRMLY UNTIL SEAL IS OPEN. TO CLOSE, SCREW THE CAP BACK ONTO THE TUBE.

DIRECTIONS FOR USE:

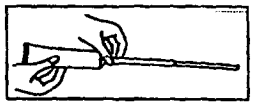
Vaginal Application

To begin the treatment, wait until bedtime. Before going to bed:

1. To open the tube, unscrew the cap.
   Turn the cap upside down and place the cap on the end of the tube. Push down firmly until the seal is broken.



2. Attach the applicator to the tube by turning applicator clockwise.

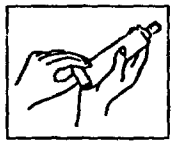


3. Squeeze the tube from the bottom.
   This will force the cream into the applicator.
   Do this until the inside piece of the applicator is pushed out as far as it will go and the applicator is completely filled. Separate applicator from tube.

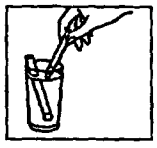
4. Hold the applicator containing the cream by the opposite end from where the cream is. Gently insert the applicator into the vagina as far as it will go comfortably.

As shown in the pictures, this can be done while standing with your feet spread a few inches apart and your knees bent. Or, you can lie on your back with your knees bent. Once you are ready, push the inside piece of the applicator in and place the cream as far back in the vagina as possible. Then remove the applicator from the vagina. You should go to bed as soon as possible after inserting the cream. This will reduce leakage. You may want to use deodorant-free minipads or pantyshields during the time that you are using miconazole nitrate vaginal cream. This is because the cream can leak and/or you may see some discharge. DO NOT USE TAMPONS.

5. After each use, replace cap and roll tube from bottom.



6. Be sure to clean the applicator after each use. Pull the two pieces apart. Wash them with soap and warm water. To rejoin, gently push the inside piece into the outside piece as far as it will go.



7. Repeat steps 2 through 6 before going to bed on each of the next six evenings.

External Vulvar Application

If needed, use the cream twice daily as follows:

1. Squeeze a small amount of cream onto your finger.
2. Gently apply the cream onto the skin (vulva) that itches and is irritated.
3. Repeat steps 1 and 2 each morning and evening as needed.

ADVERSE REACTIONS (SIDE EFFECTS)

The following side effects have been reported with the use of miconazole nitrate vaginal cream: a temporary increase in burning, itching, and/or irritation when the cream is inserted. Abdominal cramping, headaches, hives, and skin rash have also been reported. If any of these occur, stop using miconazole nitrate vaginal cream and consult your doctor.

FOR BEST RESULTS

1. Be sure to use all of the cream even if your symptoms go away before you have used all of the cream.
2. Use one applicatorful of cream at bedtime for seven nights in a row, even during your menstrual period.
3. Wear cotton underwear.
4. If your partner has any penile itching, redness, or discomfort, he should consult his doctor and mention that you are treating yourself for a vaginal yeast infection.
5. Dry the outside vaginal area thoroughly after a shower, bath, or swim. Change out of a wet bathing suit or damp workout clothes as soon as possible. A dry area is less likely to encourage the growth of yeast.
6. Wipe from front to rear (away from the vagina) after a bowel movement or urination.
7. Do not douche unless your doctor tells you to do so. Douching may disturb the vaginal bacterial balance.
8. Do not scratch if you can help it. Scratching can cause more irritation and can spread the infection.
9. Discuss with your doctor any medication you are now taking. Certain types of medication can make your vagina more prone to infection.

IF YOU HAVE A QUESTION

Questions of a medical nature should be taken up with your doctor.

ACTIVE INGREDIENT

Miconazole Nitrate 2% (100 mg per dose).

INACTIVE INGREDIENTS: Apricot Kernel Oil/PEG-6, Butylated Hydroxytoluene, Mineral Oil, PEG-6-32 Stearate/Glycol Stearate, Purified Water and Benzoic Acid (0.20%) as a preservative.

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STORAGE

Store at room temperature 15° - 30°C (59° - 86°F).
Avoid heat (over 30°C or 86°F).

Issued: May 3, 1996

Mfd. by: **Taro Pharmaceuticals Inc.,** Bramalea, Ontario, Canada L6T 1C3

PK-1365-0
000

TARO

Miconazole
Nitrate Vaginal Cream 2%
7 Day Vaginal Cream

NDC 51672-2035-6

CURES MOST VAGINAL YEAST INFECTIONS AND RELIEVES ASSOCIATED EXTERNAL VULVAR ITCHING AND IRRITATION.

TARO

Miconazole
Nitrate Vaginal Cream 2%
7 Day Vaginal Cream

NDC 51672-2035-6

CURES MOST VAGINAL YEAST INFECTIONS AND RELIEVES ASSOCIATED EXTERNAL VULVAR ITCHING AND IRRITATION.

JAN 1 8 1997

APPROVED

Full prescription strength
Educational Brochure Enclosed

NET WT 45 g (1.5 oz)
ONE TUBE OF VAGINAL CREAM & APPLICATOR (7 Day Therapy)

TARO

Miconazole
Nitrate Vaginal Cream 2%
7 Day Vaginal Cream

NDC 51672-2035-6

FPC

N 3 51672 20036 7

Miconazole
Nitrate Vaginal Cream 2%
7 Day Vaginal Cream

Miconazole
Nitrate Vaginal Cream 2%
7 Day Vaginal Cream

INDICATIONS: For the treatment of vaginal yeast infections (candidiasis) and the relief of external vulvar itching and irritation associated with a yeast infection.
Before using, read the enclosed educational brochure.
IF THIS IS THE FIRST TIME YOU HAVE HAD VAGINAL OR VULVAR ITCH AND DISCOMFORT, CONSULT YOUR DOCTOR. IF YOU HAVE HAD A DOCTOR DIAGNOSE A VAGINAL YEAST INFECTION BEFORE AND HAVE THE SAME SYMPTOMS NOW, USE THIS CREAM AS DIRECTED FOR SEVEN CONSECUTIVE DAYS

FOR VAGINAL USE ONLY. DO NOT USE IN EYES OR TAKE BY MOUTH.

DIRECTIONS: Insert one applicatorful of cream into the vagina at bedtime for seven nights in a row. Squeeze a small amount of cream onto your finger and gently spread the cream onto the affected area of the vulva twice daily (morning and bedtime) for up to 7 days as needed to relieve external vulvar itching. **THE CREAM SHOULD NOT BE USED FOR VULVAR ITCHING DUE TO CAUSES OTHER THAN A YEAST INFECTION.** Applicator and instructions are enclosed.

WARNINGS: DO NOT USE MICONAZOLE NITRATE VAGINAL CREAM IF YOU HAVE ANY OF THE SIGNS AND SYMPTOMS LISTED BELOW. ALSO, IF THEY OCCUR WHILE USING MICONAZOLE NITRATE VAGINAL CREAM, STOP USING THE PRODUCT AND CONTACT YOUR DOCTOR RIGHT AWAY. YOU MAY HAVE A MORE SERIOUS ILLNESS. • FEVER (HIGHER THAN 100°F ORALLY). • PAIN IN THE LOWER ABDOMEN, BACK, OR EITHER SHOULDER. • A VAGINAL DISCHARGE THAT SMELLS BAD. IF YOU DO NOT IMPROVE IN 3 DAYS, OR IF YOU DO NOT GET WELL IN 7 DAYS, YOU MAY HAVE A CONDITION OTHER THAN A YEAST INFECTION. CONSULT YOUR DOCTOR. If your symptoms return within two months or if you have infections that do not clear up easily with proper treatment, consult your doctor. You could be pregnant or there could be a serious underlying medical cause for your infections, including diabetes or a damaged immune system (including damage from infection with HIV - the virus that causes AIDS). (PLEASE READ EDUCATIONAL BROCHURE FOUND INSIDE PACKAGE.)

Mineral oil may weaken latex in condoms or in diaphragms. This cream contains mineral oil. Do not rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy while using miconazole nitrate vaginal cream.

• Do not use tampons while using this medication. • DO NOT USE IN GIRLS LESS THAN 12 YEARS OF AGE. • If you are pregnant or think you may be pregnant, do not use this product except under the advice and supervision of a doctor.

• Keep this and all drugs out of the reach of children. • In case of accidental ingestion, seek professional assistance or contact a poison control center immediately.

ACTIVE INGREDIENT: Miconazole Nitrate 2% (100 mg per dose).

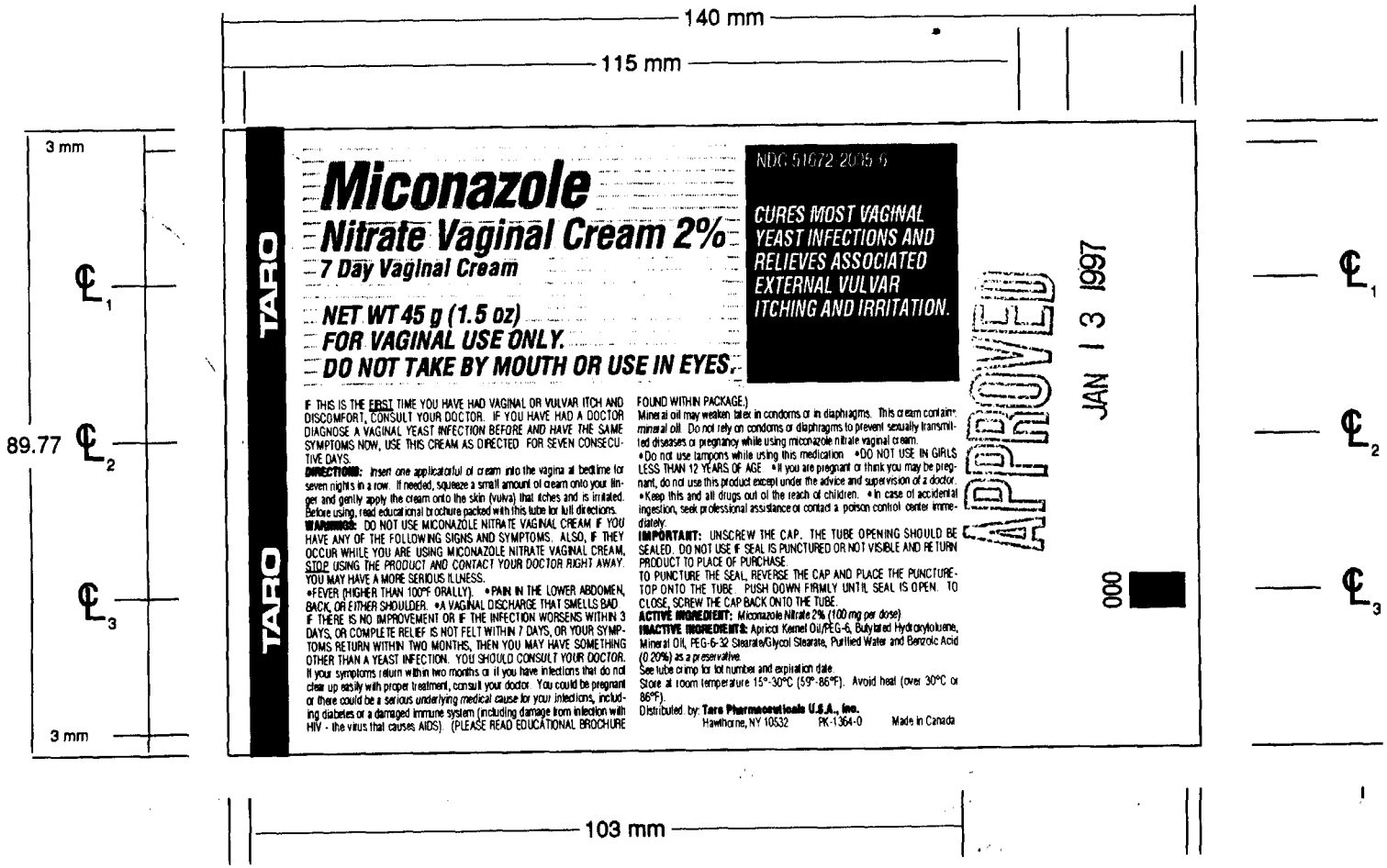
INACTIVE INGREDIENTS: Apricot Kernel Oil/PEG-6, Butylated Hydroxytoluene, Mineral Oil, PEG-6-32 Stearate/Glycol Stearate, Purified Water and Benzoic Acid (0.20%) as a preservative.

Store at room temperature 15°- 30°C (59°- 86°F). Avoid heat (over 30°C or 86°F).
For lot number and expiration date see flap of carton or crimp of tube.

IMPORTANT: UNSCREW THE CAP. THE TUBE OPENING SHOULD BE SEALED. DO NOT USE IF SEAL IS PUNCTURED OR NOT VISIBLE AND RETURN PRODUCT TO PLACE OF PURCHASE. TO PUNCTURE THE SEAL, REVERSE THE CAP AND PLACE THE PUNCTURE-TOP ONTO THE TUBE. PUSH DOWN FIRMLY UNTIL SEAL IS OPEN. TO CLOSE, SCREW THE CAP BACK ONTO THE TUBE.

Distributed by
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

Made in Canada


140 mm
115 mm
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89.77
3 mm
TARO
TARO
Miconazole
Nitrate Vaginal Cream 2%
7 Day Vaginal Cream
NET WT 45 g (1.5 oz)
FOR VAGINAL USE ONLY.
DO NOT TAKE BY MOUTH OR USE IN EYES.
NDC 51672 2035 6
CURES MOST VAGINAL YEAST INFECTIONS AND RELIEVES ASSOCIATED EXTERNAL VULVAR ITCHING AND IRRITATION.
APPROVED
JAN 13 1997
IF THIS IS THE FIRST TIME YOU HAVE HAD VAGINAL OR VULVAR ITCH AND DISCOMFORT, CONSULT YOUR DOCTOR. IF YOU HAVE HAD A DOCTOR DIAGNOSE A VAGINAL YEAST INFECTION BEFORE AND HAVE THE SAME SYMPTOMS NOW, USE THIS CREAM AS DIRECTED FOR SEVEN CONSECUTIVE DAYS.
DIRECTIONS: Insert one applicatorful of cream into the vagina at bedtime for seven nights in a row. If needed, squeeze a small amount of cream onto your finger and gently apply the cream onto the skin (vulva) that itches and is irritated. Before using, read educational brochure packed with this tube for full directions.
WARNINGS: DO NOT USE MICONAZOLE NITRATE VAGINAL CREAM IF YOU HAVE ANY OF THE FOLLOWING SIGNS AND SYMPTOMS. ALSO, IF THEY OCCUR WHILE YOU ARE USING MICONAZOLE NITRATE VAGINAL CREAM, STOP USING THE PRODUCT AND CONTACT YOUR DOCTOR RIGHT AWAY. YOU MAY HAVE A MORE SERIOUS ILLNESS.
•FEVER (HIGHER THAN 100°F ORALLY). •PAIN IN THE LOWER ABDOMEN, BACK, OR EITHER SHOULDER. •A VAGINAL DISCHARGE THAT SMELLS BAD
IF THERE IS NO IMPROVEMENT OR IF THE INFECTION WORSENS WITHIN 3 DAYS, OR COMPLETE RELIEF IS NOT FELT WITHIN 7 DAYS, OR YOUR SYMPTOMS RETURN WITHIN TWO MONTHS, THEN YOU MAY HAVE SOMETHING OTHER THAN A YEAST INFECTION. YOU SHOULD CONSULT YOUR DOCTOR.
If your symptoms return within two months or if you have infections that do not clear up easily with proper treatment, consult your doctor. You could be pregnant or there could be a serious underlying medical cause for your infections, including diabetes or a damaged immune system (including damage from infection with HIV - the virus that causes AIDS). (PLEASE READ EDUCATIONAL BROCHURE FOUND WITHIN PACKAGE.)
Mineral oil may weaken latex in condoms or in diaphragms. This cream contains mineral oil. Do not rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy while using miconazole nitrate vaginal cream.
•Do not use tampons while using this medication. •DO NOT USE IN GIRLS LESS THAN 12 YEARS OF AGE. •If you are pregnant or think you may be pregnant, do not use this product except under the advice and supervision of a doctor. •Keep this and all drugs out of the reach of children. •In case of accidental ingestion, seek professional assistance or contact a poison control center immediately.
IMPORTANT: UNSCREW THE CAP. THE TUBE OPENING SHOULD BE SEALED. DO NOT USE IF SEAL IS PUNCTURED OR NOT VISIBLE AND RETURN PRODUCT TO PLACE OF PURCHASE.
TO PUNCTURE THE SEAL, REVERSE THE CAP AND PLACE THE PUNCTURE-TOP ONTO THE TUBE. PUSH DOWN FIRMLY UNTIL SEAL IS OPEN. TO CLOSE, SCREW THE CAP BACK ONTO THE TUBE.
ACTIVE INGREDIENT: Miconazole Nitrate 2% (100 mg per dose)
INACTIVE INGREDIENTS: Apricot Kernel Oil/PEG-6, Butylated Hydroxytoluene, Mineral Oil, PEG-6-32 Stearate/Glycol Stearate, Purified Water and Benzoic Acid (0.20%) as a preservative.
See tube crimp for lot number and expiration date.
Store at room temperature 15°-30°C (59°-86°F). Avoid heat (over 30°C or 86°F).
Distributed by: Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532 PK-1364-0 Made in Canada
000
103 mm

ANDA 74-444

Taro Pharmaceuticals, Inc.
Attention: Avraham Yacobi, Ph.D.
5 Skyline Drive
Hawthorne NY 10532

DEC 13 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Miconazole Nitrate Vaginal Cream 2%.

> The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DEC 10 1996

Miconazole Nitrate
2%, Vaginal Cream
ANDA #74-444
Reviewer: F. Nouravarsani
74444MC.D93

Taro Pharmaceutical,Inc.
Bramalea, Ontario, Canada
Review Date:
December 20, 1993
October 16, 1995
October 30, 1995
November 07, 1995

REVIEW OF A MEDICAL CONSULTATION

The application was reviewed by Division of Anti-Infective Drug Products (HFD-520), for Miconazole, 2% vaginal cream (test product) used in treatment of women with vaginal Candidiasis (the review is attached).

OBJECTIVE:

1. The study (#MCN1) compared the generic test product, Miconazole Nitrate, Vaginal Cream, 2% submitted by Taro, with the reference product, Monistat-7 by Ortho USA. The test product was also compared with the Monistat-7 by Ortho Canada.

2. Compare the adverse events of the products, and establish that Taro cream does not have any unanticipated adverse events.

STUDY DESIGN:

The study was a double-blind, multicenter (6 investigator), randomized, parallel design. The products were used by patient (self-administered) for seven consecutive nights.

The patients visited two post-treatments: visit two at days 14-17, and visit 3 at days 35-42.

Patients were evaluated for Clinical efficacy, for mycological efficacy and for therapeutic outcome within 28 - 35 days after completion of the 7 day treatment regimen.

Patients were considered to be Therapeutic Failures if they were either a clinical failure and/or a mycological failure at either of the two follow up visits.

The parameters evaluated were: erythema, discharge, edema, excoriation, and itching/burning. The parameters were evaluated by a scale of 1-4, 1 for normal, and 4 for most severe.

The firm evaluated the bioequivalence of the products based on the "proportion of patients that had a mycologic cure, and separately, the proportion that had a clinical cure, using a two one-sided test procedure with confidence limits of 90%."

The following firm's definitions were accepted by the Medical Officer:

Mycologic Cure was defined: "as the absence of organisms on a KOH smear and inability to culture organisms on an appropriate culture medium" for both first and second revisits. According to the applicant: "The mycological cure rate was the primary efficacy parameter."

Clinical Cure was defined: "as the investigator physician's clinical evaluation of an improvement in symptoms at revisit one (visit 2) compared to baseline visit (visit 1), and the absence of symptoms at revisit two (visit 3)."

Safety Analysis:

All 3 products were tolerated well, and no patient was dropped due to an adverse reaction. Burning was experienced by two patients, one by using the test product, and the other one by using the Ortho Canada.

RESULTS:

The Therapeutic Cure Rate for combined clinical and mycologic cures by visit 3 was 35/50 (70%) for the test product. For the reference product, USA Monistat-7 was 47/62 (76%), and for Canada Monistat-7 was 47/64 (73%). Comparing the Taro product to the Ortho USA product by using the 90% Confidence Interval (corrected), the upper and lower limits around the difference between the two study arms were -21.5%, +9.9%. The 90% CI between the Taro and Ortho Canada products was -19.2%, +12.4%.

The clinical reviewer reanalyzed the data: The Therapeutic Cure Rate for combined clinical and mycologic cures by visit 3 was 34/50 (68%) for the test product. For the reference product, USA Monistat-7 was 45/62 (73%), and for Canada Monistat-7 was 46/64 (72%). Comparing the Taro product to the Ortho USA product by using the 90% Confidence Interval (corrected), the upper and lower limits around the difference between the two study arms were -20.7%, +11.5%. The 90% CI between the Taro and Ortho Canada products was -19.9%, +12.2%.

COMMENT:

There is a discrepancy in the clinical results and therefore Dr. Williams reanalysed the data with the help of the Clinical Devision. Further re-evaluation indicates that Taro's Miconazole Nitrate Vaginal Cream is safe, effective, and equivalent to the reference product, Monistat-7 (see attached Dr. R. William's E-mail dated 11/24/96).

RECOMMENDATION BY THE DIVISION OF BIOEQUIVALENCE:

The bioequivalence study submitted by Taro Pharmaceutical on its Miconazol Nitrate Vaginal Cream, 2%, comparing it to USA Monistat-7 has been found acceptable by the Division of Bioequivalence. The study demonstrates that Taro's Miconazol Nitrate, 2%, Vaginal Cream is bioequivalent to the reference products, Monistat-7, 2%, Vaginal Cream manufactured by Ortho USA and Ortho Canada.

From the Bioequivalence point of view the firm has met the requirements of in vivo bioequivalency, and the application is acceptable.

Farahnaz Nouravarsani

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE Ramanand M. Mhatre 12/6/96

Concur: N Patnaik Date: 12/10/96
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

FNouravarsani/11-26-96/74444MC.D93 (D93)

CC: ANDA #74-444 (original, duplicate) Nouravarsani, HFD-658, Drug File, Division File.

M E M O R A N D U M

Date: January 3, 1996

To: Director, Office of Generic Drugs
HFD-615
7500 Standish Place
Rockville, Maryland 20855

From: Julius Piver, M.D.
Medical Officer, DAIPD, HFD-520

Through; Brad Leissa, M.D.
SMO, DAIDP, HFD-520

Mary Fanning, M.D., Ph.D.
Director, DAIDP, HFD-520

Subject: Consultation on ANDA 74-444

Please find attached to this memorandum, the medical consultat from HFD-520 which was requested. If there are any questions regarding this matter, please do not hesitate to contact the Division at 827-2120.

Thank you for this consultation.

DATE SUBMITTED: DECEMBER 29, 1993
DATE RECEIVED: FEBRUARY 7, 1994
DATE COMPLETED: JANUARY 3, 1996

MEDICAL CONSULTATION FROM HFD-520
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Requested By: Division of Generic Products
HFD-615

Applicant: Taro Pharmaceuticals, Inc.

Drug: Miconazole Nitrate 2% Vaginal Cream

Drug Category: Anti-fungal

Dosage Form: Vaginal Cream

Dosage Regimen: One applicator of miconazole 2% vaginal cream inserted into the vagina each evening at bedtime for seven consecutive nights (Day 1 start).

Purpose:

The purpose of this ANDA is to obtain market approval comparable to the innovator products of a generic form of miconazole 2% vaginal cream manufactured by Taro Pharmaceuticals, Inc. for the treatment of vaginal candidiasis.
The Applicant has conducted a study comparing the efficacy and safety of miconazole 2% vaginal cream by Taro and miconazole 2% vaginal cream (Monistat 7) by Ortho Pharmaceutical Corporation USA and also Ortho Pharmaceutical (Canada) Ltd miconazole vaginal cream 2% in the treatment of vaginal candidiasis.

Background:

In the United States, vulvovaginal candidiasis continues to be one of the most frequently recurring vaginal infections diagnosed in our female population of all ages. Since the 1970's candidiasis has been safely and effectively treated by the polyenes (e.g., nystatin) and imidazoles (e.g., clotrimazole, miconazole). Miconazole is a synthetic imidazole-derivative antifungal agent that is fungicidal in vitro against species of the genus *Candida*. It is clinically indicated for the local treatment of vulvovaginal candidiasis and since 1990 has been available as an over-the-counter seven day treatment regimen.

Protocol No: MCN1

Bioequivalence of Miconazole Nitrate 2% Vaginal Cream, Taro to Miconazole Nitrate 2% Vaginal Cream Ortho U.S.A. and Ortho Canada

Study Design:

The study was a multi-center, multiple dose, double-blind, randomized, parallel comparison of miconazole 2% vaginal cream manufactured by Taro to miconazole 2% vaginal cream manufactured by Ortho USA and to miconazole 2% vaginal cream manufactured by Ortho Canada. Patients with clinically-suspected vaginal candidiasis were randomly assigned to one of three treatment groups. A KOH smear and a mycologic culture were performed on the vaginal discharge from each patient at the time of the initial visit. Patients were told to return for follow-up visits 2 weeks (1st re-visit) and 5 weeks (2nd re-visit) after the initial visit. Lesions were evaluated clinically and by fungal culture at the first and second re-visit, representing one week and four weeks after cessation of therapy, respectively.

Monitoring:

There were two monitors for the study, a medical monitor (Daniel A. Moros, M.D.), and a clinical monitor (Jacquelyn Castaldo, R.N.). The Medical Monitor reviewed all data and decided on the clinical aspects of adverse events. The Clinical Monitor reviewed all case report forms for completeness and accuracy. The investigator allowed the Taro monitor to review all case report forms and appropriate portions of the patient's office records at regular intervals during the study. The reviews were intended to confirm adherence to the protocol and the completeness of the data on the case report forms.

ENTRY (BASELINE) VISIT:
A history and physical examination were performed to establish the patient's eligibility for the study.

Inclusion Criteria: Patients who were otherwise healthy females with clinical signs and symptoms of vaginitis and positive KOH and culture for *Candida albicans* were entered into the study. To be included in the study, patients had to fulfill these inclusion criteria:

* signed informed consent
* clinical evidence of candida vaginitis
* mycologic culture positive for candida and KOH smear positive.
* all patients at least 18 years of age; no upper age limit was established.

At the entry visit, serum chemistries, urinalysis, complete blood count with differential and a pregnancy test were also performed. *Microbiological determinations* included specimens taken from an area of active lesion and a KOH prep made; mycologic culture of infected areas were taken and incubated at 37oC; patients were to be KOH and culture positive to be enrolled in the study.

Exclusion Criteria: The presence of any of the following excluded a patient from participation in the study:

* Pregnancy;
* Nursing;
* Patients with vulvovaginal infections other than Candida species -- those who tested positive for *Trichomonas vaginalis, Chlamydia trachomatis, Neisserria gonorrhoea,* or *Gardnerella vaginalis;*
* Diabetes Mellitus;
* History of allergy or sensitivity to miconazole nitrate or related compounds;
* History of abnormal liver function studies;
* Current use of any systemic or topical antifungal, immunosuppressant or antibiotic within one week of the study;
* Use of pharmacologic doses of corticosteroids;
* History of drug or alcohol abuse;
* Previous *Candida* infection within the last 3 months;
* Females with *Candida* infection who previously failed to respond to miconazole nitrate, clotrimazole or nystatin.

Patients were instructed not to take any antibiotics or to apply any other medications to the affected area for the duration of the study. Patients were to be discontinued from the study for any of the following reasons:

* Decision by the patient to leave the study for any reason;
* Ingestion or topical application of any interdicted medication;
* Development of an intercurrent condition or complication which would affect the safety of the patient or the validity of evaluation of the patient's clinical state to an extent considered significant by the investigator.

Procedure:

Once the patient signed the informed consent form and it was determined that she qualified for enrollment in the study, the following took place:

* Randomization Procedures:

  A computer-generated randomization list was used to assign patients sequentially to one of the three formulations being used. Patient numbers were assigned as the patients were entered into the study, and a supply of study drug with the corresponding number was given to the patient.

  Once a patient medication number was assigned it could not be transferred to any other patient. Additional patients were assigned consecutive patient and medication numbers as per the randomization list.

* Drug Administration:

  Patients were instructed to insert one applicatorful of the assigned vaginal cream formulation into the vagina once each day for seven (7) consecutive days, in accordance with the labeling of the product. All study creams used in this investigation were supplied by the sponsor in individual cartons containing tubes of 45 gm of miconazole 2% vaginal cream. Each patient received one 45 gm tube. All study medication was kept at room temperature prior to its use in the study. Each tube contained a standard label with the following information in English and French:
  * investigator number
  * patient number
  * protocol number

  The investigator provided the case report forms and a copy of the informed consent to Taro for each patient entered. All tubes and cartons were marked as above. Neither the patient nor the investigator knew the origin of the miconazole cream in the tube. Blinding and labeling were performed at Taro. The Taro monitor retained the randomization code in sealed envelopes.

Patient Instructions:

Patients were instructed individually in the application of the first dose of cream by the treating physician. Patients were asked to keep the infected area as clean as possible. Evaluations of the affected area were made at the initial visit to establish a baseline, and then again at the two and five week visits.

The parameters evaluated were 1) erythema, 2) discharge, 3) edema 4) excoriation and 5) itching/burning. Each parameter was evaluated on a scale of 1-4 with 1 being normal and 4 being most severe.

Patients were entered into the study only after reading, understanding and signing an informed consent. Patients were supplied with the name and telephone number of the physician to call in the event of an adverse reaction.

FIRST FOLLOW-UP VISIT: (Post treatment days 7-10 = Visit 2)

Patients were instructed to return for re-evaluation 2 weeks after initiating therapy (i.e. 1 week after completing treatment). At that time they were evaluated as follows:

* KOH and culture samples were taken of the infected area.
* Patients were instructed to return study medication at that visit.
* Patients were questioned by the investigator concerning possible adverse drug effects.
* Recording and grading of clinical signs and symptoms on a scale of 1-4 as previously described.

SECOND FOLLOW-UP VISIT: (Post treatment days 28-35 = Visit 3)

Patients returned for a second revisit three weeks after the first revisit (i.e. 4 weeks after the cessation of treatment). At this second revisit procedures were identical to those of the first revisit.

Evaluation of Efficacy Outcome

The Applicant evaluated the efficacy of the products at both the first post-treatment visit and the second post-treatment visit. The evaluation of efficacy between the three miconazole nitrate 2% vaginal creams was based on the proportion of patients that had a mycologic cure, and separately, the proportion that had a clinical cure. Mycologic cure was defined by Applicant as the absence of organisms on a KOH smear and inability to culture organisms on an appropriate culture medium. At the second revisit a patient was considered mycologically cured only if she was both culture and KOH negative at the first as well as the second revisit. Clinical cure was defined by Applicant as the investigator physician's clinical evaluation of an improvement in symptoms at revisit one (visit 2) compared to baseline visit (visit 1), and absence of symptoms at revisit two (visit 3). These definitions were accepted by the reviewing Medical Officer.

Patients were continued in the study if they had a positive culture and KOH smear with symptoms of vaginitis at entry. Those who returned for revisit 1 but not for revisit 2 were included in the data for the first revisit but were considered dropouts for the second revisit. All dropouts were considered failures. The Applicant defined the population enrolled as those women who were randomized to treatment. The evaluable population was those patients who met all inclusion and exclusion criteria at entry.

FIRST POST-TREATMENT VISIT:

Visit 2 (Day 14 of study - 7 days post-treatment - a window of 14-17 days was accepted by Applicant:

To be considered evaluable for the first post-treatment visit, patients had to have met all inclusion and exclusion criteria, and had to return for the first post-treatment visit within the 7-10 day post-treatment window. A wider window of 13-18 days was accepted by the reviewing Medical Officer to allow for weekends and holidays.

Patients were examined by their physician and the degree of clinical symptoms and lesions was recorded. KOH prep and culture samples were taken for evaluation of mycologic cure. According to the Applicant, the mycological cure rate was the primary efficacy parameter. Patients found to have a positive KOH or culture were recorded as "treatment failure" and did not need to return for visit 3.

SECOND POST-TREATMENT VISIT:

Visit 3 (day 37 of study - 30 days post-treatment - a window of 35-42 days was accepted by Applicant:

To be considered evaluable for the second post-treatment visit, patients had to have met all inclusion and exclusion criteria, and had to return for the second post-treatment visit within the 28-35 day post-treatment window. A wider window of 27-36 days was accepted by the reviewing Medical Officer to allow for weekends and holidays.

Within 28-35 days after completion of the 7 day treatment regimen, patients were re-evaluated for signs and symptoms. KOH prep and culture samples were repeated for evaluation of mycological cure. Patients were evaluated for clinical efficacy, for mycological efficacy and for therapeutic outcome.

Clinical Efficacy and Mycologic Efficacy
at Post-Treatment Visits 1 & 2

CLINICAL OUTCOME:
CURE----------resolution of all signs and symptoms of disease
IMPROVEMENT-----significant amelioration of signs and symptoms of disease
FAILURE---------persistence of signs and symptoms of disease

COMMENT: The reviewer only accepted categories of CURE *(resolution of all signs and symptoms) or* FAILURE *(persistence of any sign or symptom of disease) at the second post-treatment visit.*

MYCOLOGICAL OUTCOME:
ERADICATION-----negative KOH and negative fungal culture
PERSISTENCE-----positive KOH and/or positive fungal culture

THERAPEUTIC OUTCOME:
CURE----------resolution of all signs and symptoms of disease at the second post-treatment visit (patients had to be considered either a cure or an improvement at the first post-treatment visit also) and have negative KOH and fungal culture results at all followup visits.
FAILURE---------persistence of signs and symptoms of disease or positive KOH and/or fungal culture.

COMMENT: The reviewer considered only patients who had resolution of all signs and symptoms of disease at the second post-treatment visit (and patients had to be considered either a cure or an improvement at the first post-treatment visit) and negative KOH and fungal culture results at all visits to be *THERAPEUTIC CURES*.

Patients who were either a clinical failure and/or a mycological failure at either of the two follow up visits were considered to be *THERAPEUTIC FAILURES*.

ADVERSE REACTIONS: Any adverse reactions experienced by the patient, or noted by the investigating physician, were reported to the Clinical Monitor by telephone within 24 hours of the time the investigator became aware of their occurrence. A written report was submitted to the Clinical Monitor within 5 days. Patients were supplied with the name and telephone number of the physician to call in the event of an adverse reaction. Patients were questioned by the investigator concerning possible adverse drug effects at each revisit.

RESULTS:

Table 1
BASELINE DEMOGRAPHIC DATA

Observed	TARO N=73	Ortho USA N=83	Ortho Canada N=82	Total 238
Age (Mean)	33 yrs	33 yrs	33yrs	33yrs
HT (Mean)	64 "	65 "	65 "	65 "
WT (Mean)	136 #	137 #	136 #	136 #
Race				
White	65 (BL)	73	73	~~211~~ 207
Black	11	8	4	23
Other	1	2	5	8

According to the Applicant, there were no statistically significant differences between the three groups in age, height, weight, or racial makeup of the patients. 4 Taro patients were missing height or weight information, hence the difference between the 242 patients evaluable at baseline and the 238 patients in Table 1. The initial enrollment of 262 (BL) patients was reduced by 21 patients, seven in each of the three arms, for various "exclusions" which were not specified by the Applicant. The reviewing Medical Officer did not think the omissions were critical as far as the demographics was concerned as the number of patients was evenly divided between the three arms. These exclusions were considered, however, in Table 3 as ineligible for efficacy analysis.

Two hundred sixty-three (263) women presenting to their gynecologist with symptoms of vaginitis were enrolled and randomized for possible inclusion in the study.

A total of 176 evaluable patients with signs and symptoms of candida vaginitis, a positive mycologic culture and positive KOH smear were entered into the study by six investigators. All investigators were gynecologists, all were from Montreal. Of evaluable patients, 50 patients were treated with the Taro product, 62 patients were treated with the Ortho USA product, and 64 patients were given the miconazole cream manufactured by Ortho Canada. The Applicant adhered strictly to the protocol, especially with regard to the window of return for the patients. The reviewing Medical Officer determined that there were no additional patients to be excluded from analysis.

The curriculum vitae of each investigator was carefully reviewed and each was found to be qualified to conduct the study.

Table 2

Patients Evaluable by Applicant Taro
By 1st Followup Visit

Investigator	(Taro)	(Ortho USA)	(Ortho Can)	Total
Melvin Shore,M.D.	20/32	21/33	22/33	63/98 (64%)
Daniel Wiener,M.D.	18/24	19/25	24/26	61/75 (81%)
William Bilek, M.D.	5/17	12/18	11/18	28/53 (53%)
Melvin Guralnick, M.D.	4/6	5/6	2/6	11/18 (61%)
Janet Shinder, M.D.	2/3	3/5	4/4	9/12 (75%)
Richard Shatz,M.D.	1/2	2/3	1/2	4/7 (57%)
TOTAL	50/84 (60%)	62/90 (69%)	64/89 (72%)	176/263 (67%)

Table 3

Ineligible For Efficacy Analysis N = 87

Investigator	Pt. #	Taro/Ortho USA/Ortho Can	Reason
1. Guralnick	164	Ortho Can	2a
2. Wiener	821	Taro	2b
3. Bilek	23	Ortho Can	2d
4. Bilek	30	Ortho Can	2d
5. Guralnick	168	Ortho Can	2d
6. Guralnick	175	Ortho Can	2d
7. Guralnick	179	Ortho Can	2d
8. Shatz	492	Ortho Can	2d
9. Shore	664	Ortho Can	2d
10. Shore	665	Ortho Can	2d
11. Shore	710	Ortho Can	2d
12. Shore	711	Ortho Can	2d
13. Shore	729	Ortho Can	2d
14. Shore	736	Ortho Can	2d
15. Shore	757	Ortho Can	2d
16. Shore	762	Ortho Can	2d
17. Wiener	867	Ortho Can	2d
18. Bilek	6	Ortho USA	2d
19. Bilek	24	Ortho USA	2d
20. Bilek	44	Ortho USA	2d
21. Bilek	52	Ortho USA	2d
22. Shatz	491	Ortho USA	2d
23. Shinder	338	Ortho USA	2d
24. Shore	677	Ortho USA	2d
25. Shore	678	Ortho USA	2d
26. Shore	684	Ortho USA	2d
27. Shore	693	Ortho USA	2d
28. Shore	699	Ortho USA	2d
29. Shore	709	Ortho USA	2d
30. Shore	728	Ortho USA	2d
31. Shore	731	Ortho USA	2d
32. Shore	738	Ortho USA	2d
33. Wiener	848	Ortho USA	2d
34. Wiener	859	Ortho USA	2d
35. Wiener	864	Ortho USA	2d
36. Wiener	868	Ortho USA	2d
37. Bilek	15	Taro	2d
38. Bilek	18	Taro	2d
39. Bilek	25	Taro	2d
40. Bilek	29	Taro	2d
41. Bilek	39	Taro	2d
42. Guralnick	171	Taro	2d
43. Guralnick	180	Taro	2d
44. Shatz	489	Taro	2d
45. Shore	650	Taro	2d
46. Shore	666	Taro	2d

Table 3 -Continued

Investigator	Pt. #	Taro/Ortho USA/Ortho Can	Reason
47. Shore	681	Taro	2d
48. Shore	687	Taro	2d
49. Shore	705	Taro	2d
50. Shore	707	Taro	2d
51. Shore	712	Taro	2d
52. Wiener	836	Taro	2d
53. Wiener	841	Taro	2d
54. Wiener	856	Taro	2d
55. Wiener	858	Taro	2d
56. Wiener	882	Taro	2d
57. Bilek	41	Ortho Can	3a
58. Shore	679	Ortho Can	3a
59. Shore	683	Ortho Can	3a
60. Shore	704	Ortho Can	3a
61. Wiener	818	Ortho Can	3a
62. Bilek	22	Ortho USA	3a
63. Guralnick	173	Ortho USA	3a
64. Shinder	335	Ortho USA	3a
65. Shore	688	Ortho USA	3a
66. Shore	727	Ortho USA	3a
67. Wiener	825	Ortho USA	3a
68. Wiener	844	Ortho USA	3a
69. Bilek	9	Taro	3a
70. Bilek	35	Taro	3a
71. Bilek	38	Taro	3a
72. Shinder	336	Taro	3a
73. Shore	668	Taro	3a
74. Shore	700	Taro	3a
75. Shore	703	Taro	3a
76. Shore	722	Taro	3a
77. Shore	737	Taro	3a
78. Bilek	3	Ortho Can	3c
79. Bilek	4	Ortho Can	3c
80. Bilek	28	Ortho Can	3c
81. Bilek	32	Ortho Can	3c
82. Bilek	31	Ortho USA	3c
83. Shore	765	Ortho USA	3c
84. Bilek	19	Taro	3c
85. Bilek	42	Taro	3c
86. Bilek	49	Taro	3c
87. Bilek	53	Taro	3c

CODE: 2a Patient came for visit 1 only (1 patient)
2b Patient came for visit 1 & 2 only (1 patient)
2d Patient came too early/late for visit 2/3 (54 patients)
3a Protocol violation (inclusion/exclusion) (21 patients)
3c Negative KOH/culture @ visit 1 (10 patients)

Table 4

Exclusion From Efficacy Analysis By Applicant
N = 87

Reason	Taro	Ortho USA	Ortho Can	Total
Patient came too early or too late-visit 2/3	20	19	15	54
Protocol violation				
Antibiotic use	6	2	2	10
STD	1	5	3	9
Pregnancy	1	0	0	1
Illness (not specified)	1	0	0	1
Negative baseline culture	4	2	4	10
Patient came visit 1 only	0	0	1	1
Patient came visit 1 and visit 2 only (not a failure)	1	0	0	1
TOTAL	34	28	25	87

Table 4a

Exclusion From Efficacy Analysis
Per Investigator

Investigator (# enrolled in parenthesis)		Taro	Ortho USA	Ortho Canada	Total
Shore	(98)	12	12	11	35
Wiener	(75)	6	6	2	14
Bilek	(53)	12	6	7	25
Guralnick	(18)	2	1	4	7
Shinder	(12)	1	2	0	3
Shatz	(7)	1	1	1	3
Total	(263)	34	28	25	87

CLINICAL OUTCOME - PER APPLICANT

Table ~~6~~ 5

Mycological Cure Rate

Treatment Group	Visit 2	Visit 3
Ortho Canada	61/64 (95%)	56/64 (88%)
Ortho USA	61/62 (98%)	55/62 (89%)
Taro	46/50 (92%)	43/50 (86%)

Table ~~6a~~ 5a

Clinical Cure Rate

Treatment Group	Visit 2	Visit 3
Ortho Canada	64/64 (100%)	54/64 (84%)
Ortho USA	62/62 (100%)	50/62 (81%)
Taro	50/50 (100%)	41/50 (82%)

Table ~~6b~~ 5b

Therapeutic Cure Rate

Treatment Group	Visit 3
Ortho Canada	47/64 (73%)
Ortho USA	47/62 (76%)
Taro	35/50 (70%)

Mycological cure was defined as both KOH smear and mycological culture negative at return visits 2 & 3. Clinical cure was defined as an improvement in symptoms at visit 2 compared to visit 1 and absence of symptoms at visit 3. Therapeutic cure was defined as mycologically and clinically cured at both revisits (i.e., resolution of all signs and symptoms at visit 3 and negative KOH and fungal culture at visit 2 and visit 3).

CLINICAL OUTCOME - PER MEDICAL OFFICER

Table 7b

Mycological Cure Rate

Treatment Group	Visit 2	Visit 3
Ortho Canada	61/64 (95%)	60/64 (94%)
Ortho USA	61/62 (98%)	59/62 (95%)
Taro	46/50 (92%)	43/50 (86%)

Table 7b 6a

Clinical Cure Rate

Treatment Group	Visit 2	Visit 3
Ortho Canada	56/64 (88%)	53/64 (83%)
Ortho USA	55/62 (89%)	50/62 (81%)
Taro	48/50 (96%)	45/50 (90%)

Table 7b 6b

Therapeutic Cure Rate

Treatment Group	Visit 3
Ortho Canada	46/64 (72%)
Ortho USA	45/62 (73%)
Taro	34/50 (68%)

Mycological cure was defined as both KOH smear and mycological culture negative at return visits 2 & 3. Clinical cure was defined as an improvement in symptoms at visit 2 compared to visit 1 and absence of symptoms at visit 3. Therapeutic cure was defined as mycologically and clinically cured at both revisits (i.e., resolution of all signs and symptoms at visit 3 and negative KOH and fungal culture at visit 2 and visit 3).

Clinical Outcome Summary:

At visit 2, the Applicant demonstrated a 92% mycological cure rate for the Taro product, compared to a 95% cure rate for the Ortho Canada product and 98% cure rate for the Ortho USA product. The Medical Officer found comparable rates of 92% (Taro), 95% (Ortho Canada), and 98% (Ortho USA). At the second re-visit (Visit 3) the Applicant showed an 86% mycological cure rate for its product versus an 88% rate for Ortho Canada and 89% for Ortho USA. The Medical Officer's review demonstrated rates of 86% (Taro), 94% (Ortho Canada), and 95% (Ortho USA).

The clinical cure rates at visit 2 per the Applicant were 100% for each arm of the study. The reviewing Medical Officer's clinical cure rates at visit 2 were 96% for the Taro product, 88% for the Ortho Canada product, and 89% for the Ortho USA product. At visit 3 (2nd re-visit) the Applicant found an 82% clinical cure rate for the Taro product compared with an 84% (Ortho Canada) and 81% rate(Ortho USA) for the other two arms of the study. The Medical Officer's analysis gave comparable results of 90% (Taro), 83% (Ortho Canada) and 81% (Ortho USA).

The therapeutic cure rate for the Taro arm of the study was 70% per the Applicant versus 73% for the Ortho Canada product and 76% therapeutic cure rate for the Ortho USA product. The Medical Officer's review demonstrated 68% for the Taro product, 72% for the Ortho Canada product, and 73% for the Ortho USA product.

The therapeutic cure rate is the test-of-cure outcome parameter and the basis for approvability of all drugs for vaginal candidiasis.

Statistical analysis of the above information is necessary to determine if these figures fall within the 90% confidence interval of +/- 20% for approval.

SAFETY ANALYSIS

ACCORDING TO THE DATA PRESENTED, ALL THREE PREPARATIONS OF MICONAZOLE 2% VAGINAL CREAM WERE WELL TOLERATED. THERE WERE NO SERIOUS ADVERSE REACTIONS. TWO PATIENTS EXPERIENCED BURNING ASSOCIATED WITH THE ADMINISTRATION OF THE DRUG, ONE USING THE TARO PRODUCT, THE OTHER USING THE ORTHO CANADA PRODUCT. NO PATIENT DROPPED OUT OF THE STUDY DUE TO AN ADVERSE REACTION.

SUMMARY:

The applicant, Taro Pharmaceuticals Inc., has submitted data from a double blind, randomized, parallel group study comparing miconazole 2% vaginal cream manufactured by Taro to miconazole 2% vaginal cream manufactured by Ortho USA and to miconazole 2% vaginal cream manufactured by Ortho Canada. Based on these data, the Applicant is requesting approval of its miconazole 2% vaginal cream for the seven day treatment of vulvovaginal candidiasis.

The criterion for demonstrating therapeutic equivalence for generic drugs is that the lower and upper limits of the 90% confidence interval around the difference between the three active products must lie within the interval (-.20, +.20)

The data that have been submitted by the Taro Pharmaceuticals Inc., have been verified and analyzed by me with statistical consultation from Ralph Harkins, PhD. of the Division of Biometrics. If the statistical analysis substantiates the Applicant's claim of bioequivalency for the Ortho USA, Ortho Canada, and Taro products to each other on clinical and mycological grounds at both first and second revisits, it is my recommendation that approval be granted to Taro Pharmaceuticals Inc. for its 2% miconazole nitrate vaginal cream for the treatment of vulvovaginal candidiasis.

CONCLUSION:

On the basis of my review of the data submittd with this ANDA, it is my conclusion that the formulations of miconazole nitrate 2% vaginal cream manufactured by the Applicant, Taro Pharmaceutical Inc. and by Ortho USA and Ortho Canada are clinically equivalent for safety and efficacy in the treatment of vulvovaginal candidiasis for seven days.

RECOMMENDATION:

If my conclusion is substantiated by statistical analysis, it is my recommendation that approval be grantd to Taro Pharmaceuticals Inc. for its formulation of miconazole nitrate 2% vaginal cream, for the treatment of vulvovaginal candidiasis.

Labeling should be negotiated by the Office of Generic Drugs.

Julius S Piver M.D.

Julius S. Piver, M.D.
Medical Officer (Ob-Gyn)

Concurrence Only:
HFD/520/Dir/MFanning
HFD/520/SMO/BLeissa BL 5/24/96

Statistical Review and Evaluation
(Consult)

ANDA#: 74-444

Applicant: Taro Pharmaceuticals, Inc.

Name of Drug: Miconazole Nitrate 2% Vaginal Cream

Documents Reviewed: Medical Officer's Review and Data Transmitted January 5, 1996

Indication: Vaginal Candidiasis.

Type of Review: Clinical

Medical Input: Dr. Julius Piver, HFD-520

A. INTRODUCTION

This is a Generic Drug Product. Therefore we use the 90% confidence interval (CI) for determining therapeutic and related equivalency statements. This is the same as using two-one sided 95% confidence intervals. The allowable delta in Generic Drug trials is 20% for cure/failure type trials and within 20% of the active control mean response for other type response variables. Since the concept is that the new agent is be neither better than nor worse than the control agent, the 90% CI must be completely contained within the -20% and +20% delta values. However, in calculating Confidence Intervals below the order of subtraction between success rates is (test cure rate - control cure rate).

Generic Drug Division trials of vaginal care products are generally standardized. As a result, a full statistical evaluation of the total submission is only done if problems in conduct or reporting of trial results are noted by the Reviewing Medical Officer (RMO). When there are no problems our review is confined to checking statistical results developed by the RMO or to computing confidence intervals on data derived by the RMO. Since data is not provided us by the investigator, no evaluation of consistency among (between) investigators by treatment can be made. Therefore, if the odds ratios differ significantly among the investigators, the following evaluation will not account for this.

B. Calculations and Evaluation

The sponsor has compared their Miconazole nitrate 2% vaginal cream for the treatment of recurrent vaginal candidiasis to Ortho Pharmaceutical Corporation's Canadian and USA Monistat 7 products. In order to not penalize the sponsor by making corrections for multiple comparisons, I have chosen as the primary statistical comparison that between Taro's product and Ortho's USA product. Other comparisons are given for informational purposes.

not decisional purposes. All calculations are based on the data supplied in the RMO's January 3, 1996 Review. All confidence interval results are presented as two-sided 90% confidence intervals in the format $_{nt, nc}(CI)_{pt, pc}$. where n_t and p_t are respectively the sample size and success rates for the test agent (Taro's product) and n_c and p_c are similarly defined for the control agent (Ortho's Formulations). When comparing the Canadian formulation to the USA formulation, the Canadian formulation is the test product. The sponsor wants to demonstrate that their product is therapeutically equivalent to the Ortho USA formulation.

Mycological and clinical response rates are secondary efficacy criteria and the therapeutic response rate is the primary efficacy criteria.

For comparability of results, I have calculated 90% CIs based on the sponsor's data and the data supplied by the Medical Officer.

The following CIs are based on the sponsor's data, Tables 6, 6a and 6b, page 15 of the RMO's review.

For mycologic response at visit 2 the Taro versus Ortho USA 90% CI is $_{50,62}(-.15, .02)_{.92,.98}$ and at visit three the 90% CI is $_{50,62}(-.15, .09)_{.86,.89}$.

For mycologic response at visit 2 the Taro versus Ortho Canada 90% CI is $_{50,64}(-.13, .06)_{.92,.95}$ and at visit three the 90% CI is $_{50,64}(-.14, .11)_{.86,.88}$.

Finally, for mycologic response at visit 2 the Ortho Canada versus Ortho USA 90% CI is $_{64,62}(-.04, .10)_{.95,.98}$ and at visit three the 90% CI is $_{64,62}(-.10, .12)_{.88,.89}$.

For clinical response at visit 2 no CIs are calculated since all show 100% cure rates.

Clinical comparisons at visit three the Taro versus Ortho USA 90% CI is $_{50,62}(-.11, .15)_{.82,.81}$. Taro versus Ortho Canada 90% CI is $_{50,64}(-.16, .11)_{.82,.84}$ and Ortho Canada versus Ortho USA 90% CI is $_{64,62}(-.16, .09)_{.84,.81}$.

Therapeutic cure rate comparisons at visit three, the primary efficacy variable, the Taro versus Ortho USA 90% CI is $_{50,62}(-.21, .10)_{.70,.76}$. Taro versus Ortho Canada 90% CI is $_{50,64}(-.19, .12)_{.70,.73}$ and Ortho Canada versus Ortho USA 90% CI is $_{64,62}(-.17, .12)_{.73,.76}$.

The primary comparison of Taro versus Ortho USA for Therapeutic cure rates fails to meet the definition of therapeutic equivalency of 20% given above.

The following CIs are based on the Medical officer's data from Tables 7, 7a and 7b, page 16.

For mycologic response at visit 2 the Taro versus Ortho USA 90% CI is $_{50,62}(-.15, .02)_{.92,.98}$ and at visit three the 90% CI is $_{50,62}(-.20, .02)_{.86,.95}$.

For mycologic response at visit 2 the Taro versus Ortho Canada 90% CI is $_{50.64}(-.13, .06)_{.92..95}$ and at visit three the 90% CI is $_{50.64}(-.19, .03)_{.86..94}$.

Finally, for mycologic response at visit 2 the Ortho Canada versus Ortho USA 90% CI is $_{64.62}(-.04, .10)_{.95..98}$ and at visit three the 90% CI is $_{64.62}(-.07, .10)_{.94..95}$.

For clinical response at visit 2 the Taro versus Ortho USA 90% CI is $_{50.62}(-.02, .17)_{.98..89}$ and at visit three the 90% CI is $_{50.62}(-.03, .22)_{.90..81}$.

For clinical response at visit 2 the Taro versus Ortho Canada 90% CI is $_{50.64}(-.01, .18)_{.98..88}$ and at visit three the 90% CI is $_{50.64}(-.05, .19)_{.90..83}$.

Finally, for clinical response at visit 2 the Ortho Canada versus Ortho USA 90% CI is $_{64.62}(-.10, .12)_{.88..89}$ and at visit three the 90% CI is $_{64.62}(-.15, .11)_{.83..81}$.

For therapeutic cure at visit 3, the primary efficacy end point, the 90% CI comparing Taro to Ortho USA is $_{50.62}(-.20, .11)_{.68..73}$, the 90% CI comparing Taro to Ortho Canada is $_{50.64}(-.20, .12)_{.68..72}$, and the 90% CI comparing Ortho Canada to Ortho USA is $_{64.62}(-.14, .16)_{.72..73}$.

The primary comparison of Taro versus Ortho USA for Therapeutic cure rates meets the definition of therapeutic equivalency of 20% given above.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

At visit 3 the 90% CIs calculated using the sponsor's data fail to meet the therapeutic equivalency criteria of $\pm$ .20. However, the 90% CI calculated from the Medical Officer's data meet the therapeutic equivalency criteria. Based on this result, this trial supports the sponsor's claim of therapeutic equivalency of their product to the Ortho USA product.

Ralph Harkins PhD
1/26/96

Ralph Harkins, Ph.D.
Acting Division Director
Biomedical Statistician, Biometrics Division IV

Taro
3K/50 .68
✓ 45/62 .73
Ortho USA
-a2069 0,115

Note to Dr. J. Piver
RE: ANDA 74-444

Julius, While doing my calculations I noted some differences in % values in table 7, page 16 and the computer values. Specifically, mycological cure rate for Taro at visit 2, 46/50 = 92% rather than 90%.
Table 7a, page 16, Clinical visit 2, Ortho USA, 55/62=88.7 (89%), rather than 90% and Ortho Canada, 56/64 = 87.5% (88%) rather than 86%. Table 7b, ortho usa 45/62=72.6% (73) and Taro 34/50 = 68% rather than 70%.

ANDA 73-278

Table 7, page 18, Copley visit 3 Myco. 53/64=83% and Schering 47/55=86%, table 7a, Copley visit 2 67/68=98.52 (99%?).

Table 8, page 19, Schering visit 3, 41/52=78.8 (79%).

These do not impact calculation of CIS since I use the raw data, not %age values. It will show up if one compares the cure rates given in my CIS to what is in your tables, though.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office)		FROM:	
FD. Biometrics		HFD 520 Anti Infectives	
Jan 6, 96	IND NO. —	NDA NO. 74-444	TYPE OF DOCUMENT Medical Review	DATE OF DOCUMENT Jan 3, 1996
NAME OF DRUG Miconazole Nit. 2% Vag Cr.	PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG	DESIRED COMPLETION DAT
NAME OF FIRM TARO Pharm Inc.			

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ AVAILABILITY STUDIES
- ☐ USE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN–VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFE
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

Please calculate 90% CIs on Results of this Study of female vaginal product.

R Allecraft 1/5/96

SIGNATURE OF REQUESTER

METHOD OF DELIVERY *(Check one)* ☐ MAIL ☐ HAND

SIGNATURE OF RECEIVER Gordon Thurs 1/5/96

SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

Statistical Review and Evaluation
Addendum

ANDA#: 74-444 MAY 24 1996

Applicant: Taro Pharmaceuticals, Inc.

Name of Drug: Miconazole Nitrate 2% Vaginal Cream

Indication: Vaginal Candidiasis.

Type of Review: Clinical/Statistical

Medical Input: Dr. Julius Piver, HFD-520

The purpose of this addendum is to change the 90% confidence interval between therapeutic cure rates of Taro product and Ortho USA product.

For therapeutic cures at visit 3, the primary efficacy end point, the 90% CI comparing Taro to Ortho USA is $_{50,62}(-.207, .115)_{.68,.73}$ instead of $_{50,62}(-.20, .11)_{.68,.73}$.

Daphne Lin, 5/24/96
Daphne Lin, Ph.D.
Acting Team Leader, Biometrics IV

Concur: Ralph Harkins, Ph.D.
Division Director, Biometrics IV

cc:
Archival ANDA 74-444
HFD-520
HFD-520/Dr. Leissa
HFD-520/Dr. Piver
HFD-520/Dr. Chi
HFD-520/Dr. Harkins
HFD-520/Dr. Lin
Chron.